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(54) Title: COMPOUNDS AND METHODS FOR PROMOTING HAIR GROWTH

(57) Abstract

The present invention relates to novel pharmaceutical compositions of isoflavanoid derivatives useful for the treatment of male pattern baldness and alopecia areata, promoting the conversion of gray hair to the original pigment in hair follicles, and increasing the blood supply to the brain. The invention also relates to methods for treatment of male pattern baldness and alopecia areata, gray hair, and brain circulatory deficiencies. Also described herein are methods for the synthesis of isoflavanoid derivatives.

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Compounds and Methods for Promoting Hair Growth

The present application is a continuation-in-part of co-pending application serial no. 08/484,097, filed on June 7, 1995, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to the use of isoflavonoid derivatives for the treatment of male pattern baldness and alopecia areata, and to promote the conversion of gray hair to the original pigment in hair follicles. The invention further relates to the use of isoflavonoid derivatives to increase brain circulation, thereby alleviating symptoms associated with cardiovascular sickness resulting in decreased blood supply to the brain. Also described herein are methods for the synthesis of isoflavonoid derivatives. More particularly, this invention relates to the methods of making and using substituted benzopyranyl-4-ones.

BACKGROUND OF THE INVENTION

The management of hair loss has been addressed using topical antihypertensive agents such as minoxidil. V.H. Price, J. Amer, Acad, Dermatology, 16, 749-750 (1987). Minoxidil enlarges vellus hair follicles and seems to maintain terminal follicles in the scalps of mammals. After four months of treatment, approximately 25% of patients achieve minimal regrowth of hair. Rogaine®, the only compound approved to date to treat baldness, was developed because the oral administration of the drug stimulated hair growth. (Upjohn Co. Physicians Desk Ref., pp. 2578, 49th Ed (1995). Minoxidil is a substituted pyrimidine. The present invention relates to the use of daidzein, known as 7-hydroxy-3-(4-hydroxyphenyl)-4-H-1-benzopyranyl-4-one. Daidzein is an isoflavone with a variety of pharmacological effects.

Along with isoflavone glycosides, such as daidzin (7-glycoside daidzein), isoflavones are found mostly in

leguminous plants. (J.L. Ingham, Naturally Occurring Isoflavonoids, Vol. 43, pp. 1-226, Progress in the chemistry of organic natural products, Ed, W. Herz, H. Grisebach & G.W. Kirby, Springer-Verlag, Wien, New York, 1983). The synthesis of daidzein & its derivatives was reviewed & reported by G. Shao et al (Yao Hsueh Hsueh Pao 15(9), 538, 1980; Q.E. Ji and Y.L. Wei, Yao Hsueh Hsueh Pao 24(12), 906, 1989). They demonstrated that some of these isoflavones protected mice from hypoxia and increased their coronary blood flow. Some of the isoflavones including daidzein tested negative in mutagenicity using the Salmonella and mammalian microsomal assay (R.M. Bartholomew, D.S. Ryan, Mutat. Res. 78(4), 317, 1980).

Synthetically made daidzein was approved as a pharmaceutical agent in China in 1986 (Health Bureau of Liao Ning Province Approved Drug number; (86)772-2-2). The main indication is hypertension.

Daidzein and its derivatives were also shown to have estrogenic effects (E. Farmakalidis, Food Chem, Toxicol 22,237, 1984). In a recent study, daidzein, equol and lignan were found to compete with estradiol for binding to the rat uterine type II estrogen binding site (H. Aldercreutz et al, J. Steroid Biochem. Mol. Biol. 41(3-8): 331, 1992) and to human recombinant estrogen receptor (ibid 49(2-3): 153, 1994). The estrogenic effects are very mild and become significant only with high doses or prolonged treatment. G.H. Degan (J. Steroid Biochem 35(3-4): 473, 1990) reported that daidzein and three other isoflavones stimulated microsomal prostaglandin synthetase.

Y. Jing et al (Anti-cancer Research 13(4): 1049, 1993) reported that greater than 10μg/ml of daidzein inhibited the growth of HL60 human leukemia cells. The potent differentiation inducing activity of daidzein was also recently reviewed by R. Han (Chinese Medical Sciences. J.9(1): 61, 1994). Isoflavones, genistein, biochanin A, but not daidzein, inhibited both serum and epidermal growth

factor-stimulated growth of LNCaP and Du-145 human prostate cancer cell lines.

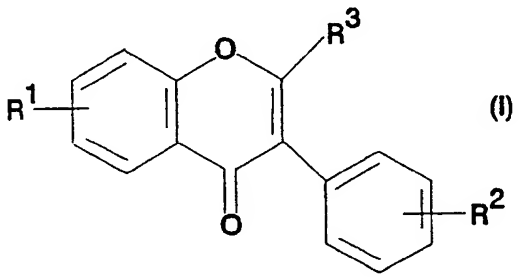
Daidzein was also shown to inhibit insulin or insulin growth factor-1 (IGF-1)-mediated signaling in cell cycle progression of Swiss 3T3 cells. It was suggested that the blocking of the G1 phase cell cycle was attributed to the inhibition of casein kinase II enzyme activity by daidzein. The enzyme is required for the commitment of mitogenic signal by insulin or IGF-1 in G1 phase. (K. Higashi and H. Ogawara, Biochim et Biophysica Acta 1221(1): 29, 1994).

Isoflavones have been claimed to exhibit antifibrile, antispasmodic, antihypertensive, and anti-dysrhythmic activities. Until recently, an effect of isoflavones on ethanol drinking behavior had never been demonstrated. In 1993, W-M Keung and B.L. Vallee published a series of studies on the implication of isoflavones, especially daidzin and daidzein, in the treatment of alcohol abuse. They found that daidzin and daidzein suppressed free choice ethanol intake, and did not significantly affect the body weight, water or food intake of Syrian Golden hamsters tested (W-M Keung and B.L. Vallee, PCT Patent Publication No. WO93/00896; Proc. Natl. Acad. Sci. USA 90:10008, 1993). This work was based on the use of folklore herbal medicine, Radix puerariae (RP) prepared from the root of leguminosae Pueraria lobota (commonly known as kudzu), for anti-drunkenness effect. RP is a rich source of isoflavones. Daidzein and genistein, isolated from RP, are reversible inhibitors of alcohol dehydrogenase (ADH) class I isozymes. The Ki of daidzein for r_1r_1 and r_2r_2 ADH isozymes is about 1μM. The inhibition is competitive with respect to ethanol, but uncompetitive with respect to NAD (W-M Keung and B.L. Vallee, Alcohol Clin. Exp. Res. 17(6) 1254, 1993; i.b.d. Prod. Natl. Acad. Sci USA 90, 1247, 1993). They reported that daidzin did not inhibit ADH; it was, however, a potent inhibitor of aldehyde dehydrogenase (ALDH) II and II of human mitochondria. They further suggested that the isoflavones could stimulate ethanol oxidation by increasing NAD^+ regeneration via accelerated

respiration because daidzein and several other isoflavones exerted significant uncoupling effect of oxidative phosphorylation *in vitro* with resting state mitochondria. (J.J.O. Lundh and B.O. Lundgren, J. Agricult, Food Chem. 39: 736, 1991).

SUMMARY OF THE INVENTION

The substituted isoflavonoids of this invention are useful in the treatment of hair loss, in the conversion of hair color to its original pigment, and in increasing blood supply to the brain, and are represented by the formula (I)



(I)

wherein R^1 represents hydrogen, hydroxy, alkoxy of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, OCOR where R is alkyl of 1-6 carbon atoms or phenyl; R^2 is hydrogen, hydroxy, alkoxy of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, OCOR where R is alkyl of 1-6 carbon atoms or phenyl; R^3 is hydrogen; and pharmaceutically acceptable salts thereof.

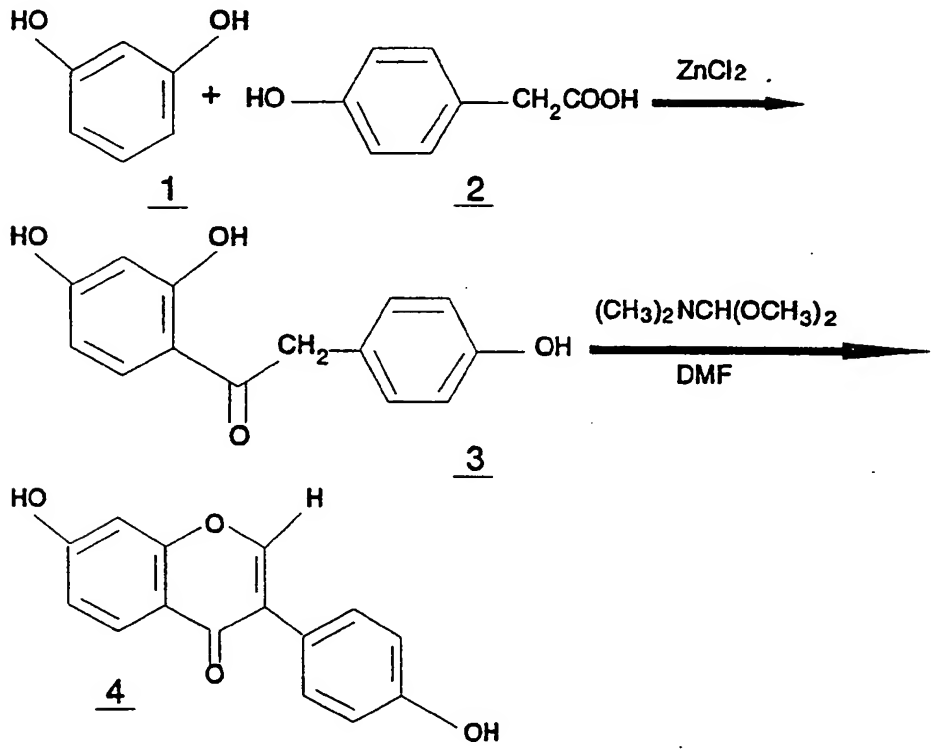
DETAILED DESCRIPTION OF THE INVENTION

Compounds of the formula (I) where R^1 and R^2 are hydroxy and R^3 is hydrogen may be prepared generally by the modification of procedures published by Iyer (R.N. Iyer, Proceed. Ind. Acad. Sci. 33A, 116, 1951) and Farkas (L. Farkas, et al., Berichte Dtsch Chem., Gcs 92, 819-821) and are hereby incorporated by reference.

As shown in Scheme I below, p-hydroxy phenylacetic acid (2) is reduced with resorcinol (1) in the presence of anhydrous zinc chloride to produce the ketone (3). Other

suitable catalysts include, but are not limited to, aluminum chloride, boron trifluoride etherate, boron trifluoride, antimony chloride and ferric chloride. The ketone (3) is treated with N,N-dimethylformamide dimethyl acetal in dimethylformamide to afford daidzein (4). The cyclization of the ketone (3) to daidzein (4) can also be effected with N,N-dimethylformamide di-tert-butyl acetal, N,N-dimethylformamide di-cyclohexyl acetal, N,N-dimethylformamide di-ethyl acetal, N,N-dimethylformamide diisopropyl acetal, and N,N-dimethylformamide di-neopentyl acetal.

Scheme I



Other isoflavonoid derivatives of the type of formula (I) exhibiting the hair growth promoting, gray hair converting, and brain blood supply increasing activities of

daidzein may be prepared by the approach of a multiple component combinatorial array synthesis by adding side chains to the daidzein core structure (R.W. Armstrong, PCT Patent Publication No. WO95/02566, published January 26, 1995), and are hereby incorporated by reference.

The present invention includes pharmaceutically acceptable salts of the compounds of formula (I). Non-toxic salts of the compounds of the above-identified formulas formed with organic or inorganic bases are also included within the scope of this invention and they include, for example, those of alkali metals, such as sodium, potassium and lithium. The salts are prepared by conventional means as, for example, by treating a compound of formula (I) with an appropriate base. Illustrative examples of compounds of this invention are shown in Table I. In addition, an extract of Pueraria lobata containing a sufficient concentration of daidzein, may also be used for the practice of the present invention.

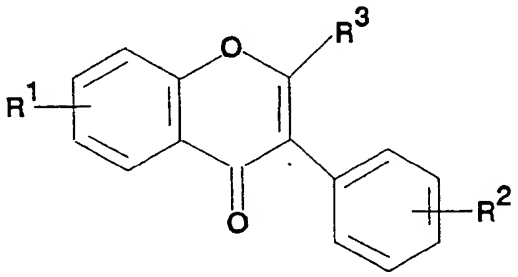


Table I

Example	R^1	R^2	R^3	M.P. (°C)
1	7-OH	4-OH	H	315-323
2	6-OH	4-OH	H	---
3	5-OH	4-OH	H	---
4	7-$OCOCH_3$	4-OH	H	---
5	7OCH_3	4-OH	H	---
6	7-OPh	4-OH	H	---
7	7-OCOPh	4-OH	H	---

Example	R^1	R^2	R^3	M.P. (°C)
8	6-$OCOCH_3$	4-OH	H	---
9	5-$OCOCH_3$	4-OH	H	---
10	7-OH	3-OH	H	---
11	7-OH	2-OH	H	---
12	7-$OCOCH_3$	3-OH	H	---
13	6-$OCOCH_3$	3-OH	H	---
14	7-OCH_3	3-OH	H	---
15	7-OPh	3-OH	H	---
16	7-OCOPh	3-OH	H	---
17	7-OH	3-OCH_3	H	---
18	7-OH	4-OCH_3	H	---
19	7-OH	4-$OCOCH_3$	H	---
20	7-OH	4-OCOPh	H	---

The compounds of this invention are useful as agents to treat male pattern baldness, to promote the conversion of gray hair to the original pigment in hair follicles, and in the treatment of brain circulatory deficiencies. In a specific embodiment, the present invention is directed to a method of increasing blood flow to the brain by the administration of an effective amount of daidzein or mixture of compounds of formula I. The compounds may be administered with suitable pharmaceutical carriers and can be in solid or liquid dosage form such as tablets, capsules, powders, soft gels, solutions, suspensions, emulsions, creams or ointments. A further object of this invention is to supply the compounds of this invention in a controlled-release formulation.

The compounds of this invention can be administered orally, parenterally, for example, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation or by application to mucous membranes via an aerosol spray or by application to the scalp or skin by ointment or a cream.

The quantity of compound administered will vary depending on the patent and the mode of administration and

can be any effective amount. The quantity of compound administered may vary over a wide range to provide in a unit dosage an effective amount from about 0.001 to 20 mg/kg of body weight of the patient per day to achieve the desired effect. For example, the desired affect can be obtained by consumption of a unit dosage form such as a tablet containing 1-200 mg of a compound of this invention taken 1-3 times daily.

A further object of this invention relates to a method of producing tablets of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one.

Tablets of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one have various clinical applications in treating central nervous system and hypertension diseases such as faintness, dizziness, stress, hand and leg numbness. They can also reduce whole blood viscosity, and reduce resistance in peripheral blood vessels. They also increases blood transport capacity and improve blood supply to certain organs. The active ingredient, 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one is non-toxic.

However, the bioavailability of tablets of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one produced in the past was not optimal due to their slow dissolution rate and the large size of the crystal of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one produced by recrystallization in ethanol (L.J. Tang, P.X. Qiao, L.Y. Zhang, Yao Hsueh Hsueh Pao 24(10): 778, 1989; Table II). The tablets taken by subjects in Examples 3, 4 and 5 were made of 100 mg of nonpulverized daidzein crystals, starch (main excipient), dextrin and magnesium stearate.

An object of the present invention is to provide a method of producing tablets of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one. The tablets made by the method of the present invention may manifest improved bioavailability and demonstrate a significant clinical effect.

A method of the present invention comprises pulverizing the raw material of the active ingredient, such as a powder of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one produced by the synthetic process described herein, to a microcrystalline product with a particle size not greater than 4 microns (Table II), mixing with an appropriate amount of carrier such as lactose, vitamins, starch, microcrystalline cellulose, disintegrant (dicalcium phosphate), inorganic salts, solubilizer and a surfactant (e.g. Tween 80), agglomerating and drying the mixture, adding magnesium stearate (lubricant), and forming tablets as described in Modern Pharmaceutics, G.S. Barber and C.T. Rhodes (1979) (Marcel Dekker, Inc. New York, NY). The pulverized raw materials along with the appropriately chosen excipients should increase the bioavailability of the formulated tablets significantly.

Table II

Down-Sizing Daidzein Crystals with Airjet Pulverizer*

Before Processing	40.8 um+
After Processing	3.81 um

* The Airjet Pulverizer (Model QS 50: 0.85/10) used to downsize the daidzein crystals was purchased from the No. 3 Chemical Engineering Mechanical Instrument Factory, Shanghai, China.

+ The Average size of the crystals examined under the microscope. um: micrometer.

Example 1

A: Preparation of dimethylamino-methoxy-sulfuric acid methyl ester

10 ml of dimethylformamide is added to 12 ml methyl sulfate. The resulting solution is allowed to react at 65° to 70°C for 2 hours.

B: Preparation of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one.

Sodium methoxide (35%) 6.48g is added into 50 ml dimethylformamide. The mixture is distilled to eliminate methyl alcohol. The resulting product is cooled to less than 20°C. Dimethylamino-methoxy-sulfuric acid methyl ester is added dropwise to the cooled product. The mixture is allowed to react for 5 hours. Under reduced pressure, the reaction mixture is subjected to distillation to remove the dimethylformamide from the mixture. Water is then added to the reaction mixture which yields 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one as a crude product. The crude product is recrystallized from ethanol. 7.62g of 7-hydryoxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one is obtained. Yield: 60%; mp: 315-323°C.

Example 2

• Active ingredient (particle size: 4 microns or less)	100 mg
• Lactose	50 mg
• Starch	23 mg
• Microcrystalline cellulose	2 mg
• Dicalcium phosphate	30 mg
• Surfactant	trace
• Magnesium stearate	trace

Pulverizing the raw material of 7-hydroxy-3-(4-hydroxy-phenyl)-4-H-1-benzopyranyl-4-one produces a microcrystal with a particle size of no more than 4 microns. The tablets are formed by adding to the pulverized or untreated daidzein the appropriate amount of fillers, solubilizer, disintegrating agents or binding agents, such as, lactose, vitamins, starch, inorganic salts, microcrystalline cellulose and a trace of surfactant to make a soft product, agglomerating the soft

product, drying the agglomerated product at 80° to 90°C, adding magnesium stearate (lubricant) to the dried product which results in the formation of tablets.

Example 3

A hypertensive male Chinese patient (age 72) complained of dizziness and heavy headiness before taking the daidzein tablets. After taking the medicine (oral dosage: 2x100 mg per dose, 3 doses per day) for four months, it was observed that he experienced a significant improvement of his symptoms, and became more mentally alert. In addition, it was discovered that a significant portion of his gray hairs had gradually turned into the original pigment or dark brown color.

Example 4

A healthy Chinese male subject (age 61) with normal blood pressure volunteered to take the medicine for observation on hair growth promoting activity at the same dose reported in Example 3. Before taking the medicine he had few hairs left in the frontoparietal area of the head. Three months after taking the medicine, he began to note an increase of hair density in the affected area. During the three to six months of the testing period, he further noted that he had to increase the hair cut frequency to once a month from once every two months. The newly grown hairs in the affected area are mostly dark brown. The response to the medicine is more sensitive in areas with most recent hair loss. The overall increase of the hair density in the affected area is very significant. The observation was terminated at the end of six months. During the observation period, the subject did not experience any untoward effects.

Example 5

A healthy Chinese male (age 47) with normal blood pressure volunteered to take the medicine for the same observation as in Example 4 at the dose described above. His

hair condition is normal with no baldness. During the six month testing period, he collected in intervals the hair samples from regular daily combing. Before the testing and during the first month of testing, the hair samples collected had two types, namely completely dark brown or completely gray. At around 50 days into the testing period, a new type of hair, partly dark brown and partly gray, began to appear in the hair samples; they represented about 3% of the gray hairs. In this subject, the gray hairs represented about 25% of his total hairs in the samples collected. It is noted that the dark brown part of the new type of hair is always associated with the lower part of the hair shaft. This is easily identifiable because the hair follicles are distinguishable at one end of hair shafts. The quality and thickness of the new type of hair is very similar to the other types of hairs of this subject. The ratio of length of the dark brown part to that of the gray part of the new type of hair varies from 1:5 to 4:1 in the samples collected during the five-month period. This varying ratio may reflect the stages of the growth cycle of each hair follicle examined. The observation was discontinued at the end of five months. No untoward effects were reported.

Example 6

Seven patients with hypertension (Stage II and III) were given 100 mg of daidzein orally three times a day for 4 to 5 weeks. The blood pressure, pulse rate, blood chemistry and symptoms of patients were monitored weekly. The arterial blood flow volume (milliliters/second) on the right and left sides of the neck of each patient was measured at the diagnosis and immediately after completion of the course of treatment with a Doppler Quantitative Instrument. As shown in Table III, the mean value of the arterial blood flow on both sides of the neck of the treated patients was significantly increased (28 to 30%); this improvement is statistically significant by paired Student t-Tests (right side comparison, p=0.019; left side comparison, p=0.024). In

patients #3 and #5, the ratios of the right side and the left side of the neck blood flow were equalized after the treatment (Patient #3, before treatment: the ratio = 1.41 vs. 1.02 after treatment; Patient #5, before treatment: the ratio = 1.43 vs. 1.02 after treatment).

Each patient also experienced significant improvement (Table IV) of several symptoms, such as headaches, giddiness, chest tightness, mental alertness and vertigo, which are frequently associated with cardiovascular sickness; some of these improvements may be attributed to increased and equalized blood supply via the neck arteries to the brain during treatment with daidzein.

Table III

BLOOD FLOW OF NECK ARTERIES (ml/Sec)

	Right Side		Left Side	
Patient #	Before Treatment	After Treatment	Before Treatment	After Treatment
1	2.70	5.79	2.29	4.68
2	4.07	4.32	4.14	5.12
3	4.39	5.09	3.12	5.00
4	4.64	6.17	5.89	5.40
5	4.40	6.59	6.31	6.54
6	3.95	5.64	3.21	5.54
7	6.51	6.45	5.81	7.10
mean ± S.D.	4.38 ± 1.13	5.72 ± 0.80	4.40 ± 1.60	5.63 ± 0.88
paired t - test	p = 0.019		p = 0.024	

Table IV

PATIENT INFORMATION

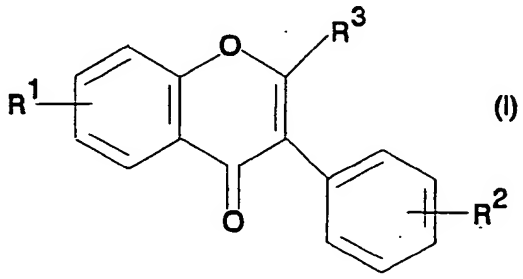
Patient #	Age	Sex	Significant Improvement of Reported Symptoms
1	64	M	headaches, insomnia, numbness of extremities
2	71	M	headaches, vertigo, mental alertness, shortness of breath
3	66	M	vertigo, chest tightness, shortness of breath
4	76	M	vertigo
5	68	M	sudden and brief loss of eyesight of the right eye
6	66	M	insomnia
7	60	M	giddiness, shortness of breath, mental alertness, fatigue, headaches, unsteady gaits

The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of individual aspects of the invention. Indeed, various modifications for the invention in addition to those shown and described herein will be come apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

All publications cited herein are incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an effective amount of a compound of formula (I) and a pharmaceutical carrier;



wherein R^1 is hydrogen, hydroxy, alkoxy of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, OCOR where R is alkyl of 1-6 carbon atoms or phenyl; R^2 is hydrogen, hydroxy, alkoxy of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, OCOR where R is alkyl is 1-6 carbon atoms or phenyl; R^3 is hydrogen; and pharmaceutically acceptable salts thereof.

2. A pharmaceutical composition of claim 1 where R^1 is hydrogen or alkoxy of 1-6 carbon atoms, R^2 is hydroxy or alkoxy of 1-6 carbon atoms and R^3 is hydrogen

3. A pharmaceutical composition of claim 1 where R^1 is 7-hydroxy, R^2 is 4-hydroxy and R^3 is hydrogen.

4. A pharmaceutical composition of claim 3 wherein the carrier is an ointment.

5. A pharmaceutical composition of claim 3 wherein the carrier is a cream.

6. A method of promoting hair growth by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 1.

7. A method of promoting hair growth by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 2.

8. A method of promoting hair growth by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 3.

9. A method of promoting hair growth by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 4.

10. A method of promoting hair growth by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 5.

11. A method of converting gray hair to the original pigment in hair follicles by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 1.

12. A method of converting gray hair to the original pigment in hair follicles by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 2.

13. A method of converting gray hair to the original pigment in hair follicles by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 3.

14. A method of converting gray hair to the original pigment in hair follicles by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 4.

15. A method of converting gray hair to the original pigment in hair follicles by treating a patient in need thereof which comprises administering to said patient an effective amount of a pharmaceutical composition of claim 5.

16. A method of increasing the blood supply to the brain to relieve brain circulatory deficiencies by treating a patient in need thereof which comprises administering to said patient an effective amount of pharmaceutical composition of claim 1.

17. A method of increasing the blood supply to the brain to relieve brain circulatory deficiencies by treating a patient in need thereof which comprises administering to said patient an effective amount of pharmaceutical composition of claim 2.

18. A method of increasing the blood supply to the brain to relieve brain circulatory deficiencies by treating a patient in need thereof which comprises administering to said patient an effective amount of pharmaceutical composition of claim 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/08433

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 43/16; A61K 31/35
US CL :514/456
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Registry, CA Previews, CA, USPAT, Medline, Biosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. WINDHOLZ et al., "DIADZEIN", The Merck Index 10th Edition, published 1983 by Merck & Co., Inc. (N.J.) page 2795.	1, 3
X -- Y --- A	Chemical Abstracts, issued 1982, Farukosu, "Cosmetics containing isoflavone derivatives", abstract no. 100:126730, JP 58225004, see entire abstract.	1-3 ---- 4-5 ---- 6-10
Y -- A	Chemical Abstracts, issued 1993, Hakamata et al., "Isolation of pterocarpene and isoflavonone derivatives from Platymiscium sp. and Swarzia sp. and anti-male hormone agents containing them", abstract no. 119:146570, JP 05078347, see entire abstract.	1-5 ---- 6-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
12 AUGUST 1996

Date of mailing of the international search report
05 SEP 1996

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/08433

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, 6-10

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/08433

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1-5, 6-10, directed to a compound and a method of promoting hair growth.
Group II, claims 11-15, directed to a method of converting gray hair to the original pigment
Group III, claims 16-18, directed to a method of increasing blood supply to the brain to relieve brain circulatory deficiencies.

The claims do not meet the requirement for unity of invention under PCT Rules 13.1 and 13.2.
Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Rule 13.2 states that Rule 12.1 shall be filfilled only when involving one or more of the same or corresponding special technical features. In the instant application the claims are to a composition and 3 methods of using said composition. Said methods do not involve the same technical features.
Rule 13.2 states that Rule 13.1 shall be fulfilled only when involving one or more of the same or corresponding special technical features.